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# **Biological Response to Blast Overpressure:**

## *A Summary of Modeling*

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### *Technical Report*

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## **Abstract**

A soldier in training is exposed to a variety of blast sources that can adversely affect his auditory and nonauditory systems. While auditory standards have been formulated for many decades, knowledge about nonauditory effects of blast have not been captured in a criteria that can be applied to all circumstances. For the past 15 years, JAYCOR, working together with the Walter Reed Army Institute of Research, has been using modeling, simulation, and data analysis to determine the nature of injury in animal models, capture that understanding in physiologically correct mathematical models, and extend the findings to objective criteria that can be used to set exposure limits. This paper summarizes the accomplishments of that effort.

# Introduction

## Background

In the course of training, the soldier is exposed to a variety of blast sources (small and large caliber), in a variety of surroundings (in the open and inside enclosures), and for single and multiple rounds. The Surgeon General of the Army must set conditions that limit the exposure of troops to blast overpressure (or "weapon noise") that will result in only a very small incidence of deleterious effects in the soldier population.

Military Standard 1474C (1991) provides rules for determining exposure limits based on auditory hazard. The data used to formulate these limits came from small caliber (high frequency) fire. The Standard assumes that the blast field can be characterized by two parameters: the peak pressure and a time duration. Based on those two quantities, a maximum number of exposures is determined. If the combination of quantities exceeds the "Z-line," the Standard allows no exposures because of unspecified nonauditory danger.

When an exposure exceeds the Standard's nonauditory limits, man-rating studies must be conducted to establish exposure limits on a weapon-by-weapon basis. This is a time-consuming and expensive procedure that is likely to become more and more common as weapon power increases. Furthermore, when the blast overpressure hazard arises in an enclosure, the variation and permutations of the exposure become so enormous that case-by-case studies are not feasible.

When blast overpressure levels increase further, the concern switches from identifying threshold to anticipating soldier performance and effectiveness. Here, the guidance for Army doctrine has come from animal tests, largely concerned with lethality estimates. More recent animal tests and more thorough analysis of previous test data reveals that physiological effects are present at much lower values than had been previously thought and involve all of the body's air-containing organs.

Finally, animal studies that consider the effects of combined trauma have shown that the pathophysiological consequences can be profound, and could have implications both for the individual and for the medical care system. Once again, the elements entering such estimates do not properly reflect what is known about the physiological consequences of blast overpressure, nor is enough known to be able to confidently anticipate the consequences.

## Previous Work

*Animal Tests.* Over the past 15 years, tests have been conducted at the Albuquerque Overpressure Test Site, under the sponsorship of the US Army Medical Research & Materiel Command (MRMC), exposing animals to blast loading. See Richmond, et al (1982), Dodd, et al. (1985), Yelverton, et al. (1993a), and Yelverton, et al. (1993b). Configurations included explosives detonated in the open and in enclosures and simulations of weapons fired from enclosures. The tests were conducted as studies with specific, narrow goals and the results were not systematically organized and analyzed in total.

Much of the experimental design was based on the assumption that respiratory injury had the lowest threshold and that injury to the upper respiratory tract preceded injury to the lung. An analysis of threshold injury levels, however, based on a preliminary compilation of the animal data showed an unexpected prevalence of injury to the GI tract and no significant difference in threshold between any of the air-containing organs. See Stuhmiller (1990).

*Injury Mechanisms.* Since the lung had been identified initially as the most critical major organ injured by blast overpressure, work was conducted to understand the mechanical properties of lung materials, so that models could be constructed. See Fung, et al. (1985). In addition, a theory was advanced connecting tissue damage to the compression wave within the lung. Fung, et al. (1988).

Using the knowledge of the biological material properties, a mechanical model of the thorax wall and lung parenchyma was developed (Yu, 1990). These studies elucidated the reasons why pressure measurements differ between the large airways and the parenchyma. Furthermore, a linear relation was observed between the velocity of the chest wall and the strength of the internal compression wave. This pivotal finding was also confirmed with mathematical simulations (Vander Vorst and Stuhmiller, 1990).

As concern over GI tract injury grew, exploratory work was undertaken to identify the underlying mechanisms. Surrogate models revealed that damage to the tract arises from concentrations of stress at locations near air bubbles (Vasel, et al., 1990). Once the mechanism was understood, the mechanical properties controlling this phenomena could be identified and experiments conducted to determine the values of these properties in small animal intestines (Yu and Vasel, 1990). A surgical procedure was developed for an isolated, perfused model of the rabbit gut in which systematic studies could be conducted (Yu, et al., 1991).

*Mathematical Modeling.* The first biomechanical models to predict response to blast overpressure were developed by White, et al. (1971). The model was calibrated to predict the esophageal pressure observed in large animal tests, but attempts to correlate this quantity with lethality were unsuccessful. Later, Josephson et al. revisited the model and concluded that the predicted pressures could not be correlated with injury. Stuhmiller (1986) showed that the empirical correlation of injury with hyperbolic curves on a peak pressure-duration axes are related to the amount of irreversible energy loss in mass-spring-damper systems. These "generic" models formed a theoretical basis from which current biomechanical models, such as Viano and Lau (1988) have been developed.

The first systematic application of this biomechanical approach was made for the tympanic membrane (Stuhmiller, 1989). Finite element modeling was used to transform the geometric details of the membrane and support structures into a mass-spring-damper system. Rupture of the membrane was associated with exceeding the tensile strength of the membrane fibers. The resulting model provided an excellent correlation of observed tympanic membrane rupture in isolated specimens. A summary of the biomechanical modeling approach and its potential for blast overpressure related problems is found in Stuhmiller, et al., (1990).

*Hazard Assessment.* As mentioned earlier, the military standard for occupational exposure is primarily one for auditory effects. A nonauditory limit was proposed that is a parallel curve with peak pressures increased by about a factor of 2. For combat casualty purposes, a lethality criteria was developed by Bowen empirically based on animal data. A "threshold" injury curve was proposed that is a parallel curve with peak pressures reduced by a constant factor. Subsequent data analysis has shown that injury occurs at peak pressures less than these "threshold" estimates.

To provide a better criterion, Dodd, et al. (1990) proposed a peak pressure-duration curve to define conditions that would not produce "unacceptable" injury (any injury to the lung or GI tract or more serious injury to the URT). Separate curves were developed for multiple exposures. These relations have been used by MRMC as an interim criterion for making health hazards assessment of free-field weapon exposures.

All of the relations based on peak pressure and duration become unreliable in enclosures because reverberations make the duration so long that extreme injuries are always predicted. Attempts to find "equivalent" free-field waveforms are scientifically unjustified and have produced equally unreliable results. Consequently, MRMC began to experiment with using JAYCOR's "generic" models to assess complex wave exposures.

In addition, the complex nature of blast waves in enclosures produces pressure traces that differ significantly from one location to another (because of the additions and cancellations caused by the myriad of wall reflections). The traces at a particular location also differ significantly depending on whether an animal is present or not (because of the shielding and amplifying effects of the body). These variations are further confounded by the shot-to-shot variations seen in repeated tests.

## **Open Issues**

Despite the considerable number of animal tests that have been conducted and the progress made in understanding the origin and mechanisms of damage, there are still questions that must be answered in order to obtain a satisfying and reliable assessment of hazard. First, in order to focus research effort, it is necessary to determine which organs are most susceptible, how severity increases with blast strength, and what aspects of blast correlate with these injuries. Second, since each new weapon produces a seemingly different blast signature, it is necessary to find a unifying approach that will anticipate and interpret new environments. Third, in order to determine the limits of biomechanical modeling to predict injury, a full validation of a single model must be made against all of the observed data. Finally, in order for the research to impact occupational exposure standards, a methodology is needed for making health hazards assessment that provides estimate of population effects and provides an estimate of error.

## **Objectives of Work**

To address these issues, four objectives were set for the work. The first is to organize all of the animal data that has been collected at the Blast Overpressure Test Site in a form that can be used to determine the susceptibility of all organ systems to blast overpressure. The second is to evaluate computational fluid dynamics (CFD) as a unified approach to predicting and interpreting blast in complex geometries. The third is to develop and validate a biomechanically-based, predictive model of gross lung injury that can be applied in all blast environments. The final objective is to develop a methodology for assessing hazard that provides an estimate of risk to the population, including estimates of confidence based on the statistical uncertainties of the animal data and of pressure measurements.



# Results

## Animal Pathology Database

The combined data from 15 years of animal testing under MRMC sponsorship is massive. A single test may contain megabytes of transient pressure data, hand written logs, documents, pathology reports and photographic images. To make it more manageable, all of the data has been converted to electronic format, including relational databases containing test conditions and pathology results, compact binary files of pressure traces, and bit map images of photography. Even in compacted form, the data from over 1000 tests occupies several hundred megabytes.

Over the 15 years, the scoring of pathology has changed. Earlier tests described pathologies in descriptive terms and small lesions were usually ignored. In recent studies, the scoring has become more quantitative and the smallest lesions are noted. To provide a uniform system by which all data could be compared, a subjective scoring system was developed that closely followed the rules used by the original investigators. All incomplete entries were re-graded using photographic records and necropsy note sheets. Investigators at the Walter Reed Army Institute of Research (WRAIR) reviewed and approved the re-grading.

In the most recent animal tests, the sophistication of the pathology scoring has become so great that almost 2000 quantities are recorded. Furthermore, this scoring system is now being used by a world-wide network of investigators. To ensure that the grading is kept uniform among all investigators, all quantities were assigned a range of specific responses with detailed definitions. To make the data collection, data merging, and data analysis processes feasible, the PATHOS 2.0 software package was developed. This software is a MS-Windows program that allows data entry, form generation, and general searches. (Masiello and Long, 1995)

A similar evolution of practice in recording blast trace data has occurred over this time. Earlier pressure data were often noted in the test logs, while recent data is collected electronically and preserved at full resolution. In qualifying the earlier blast data, many errors and omissions were discovered. Where the original data still existed in analog, digital, or printed form, the data was transferred to electronic format and re-analyzed. In many of the older free-field data, records were completely lost so an elaborate correlation of blast wave parameters had to be developed. See (Masiello and Ho, 1993)

*Data Retrieval.* To understand and effectively analyze the data being generated in the complex wave tests, it must be organized and integrated. In 1991 alone, MRMC sponsored over 50 field tests using over 120 sheep to study complex waves. These tests were run with over 25 configurations of the test bunker. Each configuration has 9 to 12 pressure gauges, the Blast Test Device, and as many as three sheep. Knowledge of the position and orientation within the bunker of each animal and gauge is critical to understanding the test results.

To access the hundreds of megabytes of data in the pathology database, an Integrated Information SYstem Software (IISYS) interface was developed. IISYS is a JAYCOR-developed information management system, running in MS Windows, for data that is primarily context related. Database records, blast traces, or photographs can be found and retrieved by pointing and clicking on diagrams. See Figure 1. The data can be processed by viewers or imported into other analysis programs such as Microsoft EXCEL.

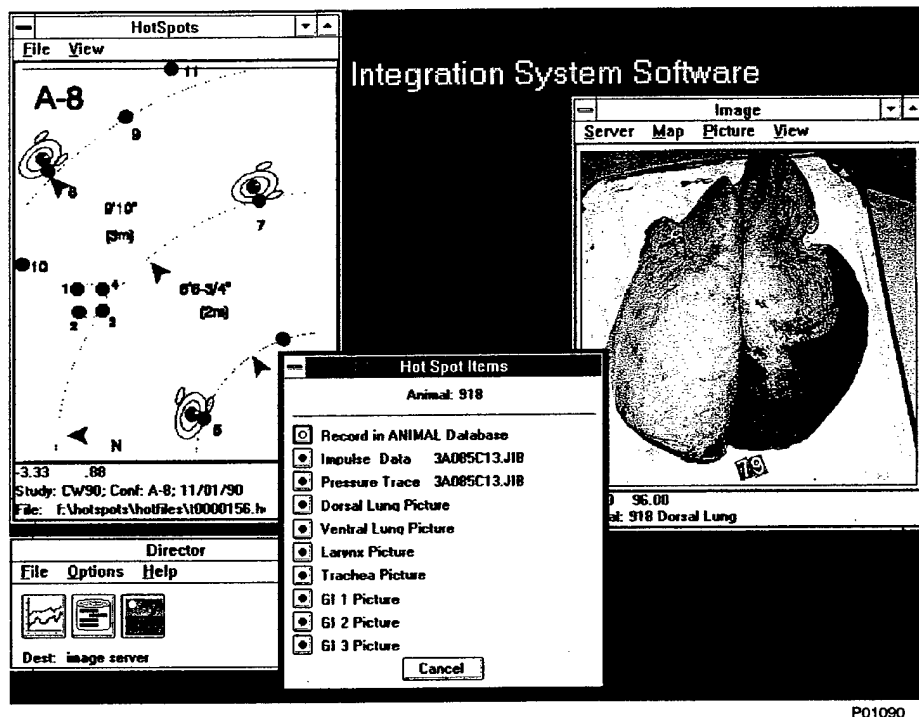


Figure 1. Screen from IISYS data management program linking test schematic diagram with pathology photography stored on compact disc.

## Data Analysis

While the biomechanical models will provide the understanding and predictive ability to anticipate all forms of blast injury, those models are still undergoing development and testing. Some organs, such as the gastrointestinal tract, are emerging as primary injury sites, but the corresponding models are only partially developed. It is important to evaluate the whole spectrum of blast injury at this time, independently of modeling considerations, so that the trends and relative importance can be assigned.

A extensive statistical analysis of the entire blast pathology database was performed to determine the injury thresholds and trends in the absence of specific biomechanical models (Stuhmiller, et al. 1995c). The trend of injury to the trachea for 20 exposures in the free-field increases with explosive energy (Figure 2). A general damage criteria was developed based on dimensional analysis and generic structural response that identified three principal dimensionless variables: the distance normalized explosive energy (EBAR), the animal weight normalized explosive weight (NCHWT), and the number of repeated exposures (NS). Multiple logistic regressions were estimated with maximum likelihood methods. Regression equations were developed for each major organ system and for each independently graded anatomical section.

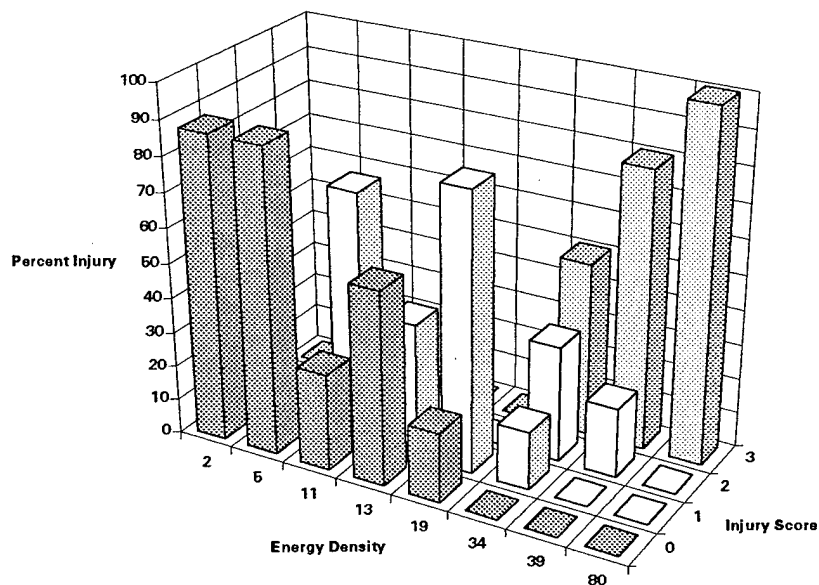


Figure 2. Statistical progression of injury to the trachea from increased energy density in the blast wave (EBAR).

Several general conclusions were found. Most free-field data correlated with EBAR, while most tests in enclosures correlated with NCHWT. This result may be due to the relatively small distance variations in enclosure tests and the influence of wall reflections. Where the data were sufficiently reliable, all major air-containing organs had statistically similar thresholds, while the solid organs had higher thresholds. Injury to all of the major organs increased with the number of exposures. The diaphragmatic lobes of the lung are the most susceptible. Injury to the lung is predominantly on the side facing the explosive in the free-field, but is without orientation preference in enclosures. Finally, the large colon is the most easily injured hollow GI organ.

## **Blast Field Simulation**

The characterization of the blast field is critical to any methodology that will estimate hazard. Only in the absolute absence of reflecting surfaces can the blast field be described by the magnitude of the explosive and the distance to the target. Even with a perfectly flat ground plane, the blast becomes a single, horizontally traveling wave (the Mach Stem) close to the ground, bounded by the so-called triple point curve, and a complex mixture of waves above the triple point curve. In an enclosure, the blast field varies with every geometry and surface reflectivity nuance. Simulations were performed using the EITACC computational fluid dynamics program of each relevant geometry that was encountered both to test the accuracy of the technique and to guide interpretation of the test results. A version of EITACC was installed at WRAIR to assist the Army in making blast field evaluations. (Masiello and Long, 1993).

*Free-field Blast Waves.* The most common blast environment arises from detonations at finite heights above the ground. To interpret the data reported in the literature, simulations were made at a variety of conditions. The results were validated against measured triple point locations and peak pressures and duration. The work showed that the blast did not follow simple scaling rules at close distances and that the region near the triple point was extremely complex. (Masiello and Ho, 1993)

Another relatively simple blast geometry arises from explosions inside a cylindrical tube. Examples include shock tubes used in laboratory experiments and the blast from large caliber weapons (without a muzzle brake). Simulations show that the blast decreases strongly with angle from the axis of the tube. Directly ahead of the tube a strong shock

forms (the Mach disk) surrounded by a vortex flow that can persist for a considerable distance. (Kan, 1994c).

Another commonly encountered blast source in the free-field is the shoulder fired weapon. Although the magnitude of the explosion is much smaller than for large howitzers, the soldier is much closer to the weapon. Furthermore, the blast emanates from both the front and rear of the weapon, making for an even more complex wave pattern. Simulations were made of the Ranger Anti-Armor Weapon System (RAAWS) as it is used in training. The results showed that the distance from the ground controls the timing of wave reflections and the occurrence of local, large pressure regions. (Klein, et al., 1994).

*Near-to-Far Field Transition.* Earlier studies of the blast field around the M198 howitzer (Stuhmiller, et al., 1981) showed that at a distance of tens of feet from these large weapons, the blast field could be simulated as the superposition of one-dimensional waves that varied in strength with angle. This angular variation was also seen in the shock tube tests. A mathematical investigation was made to determine how the near-field, complex blast pattern around a weapon evolves into the simple one-dimensional waves seen in the far-field. A criterion was developed for determining how to make this transition. (Kan and Stuhmiller, 1995)

*Enclosures.* The simplest circumstance producing complex blast waves is the detonation of an explosive in a rectangular room. Even with the greatest amount of geometric symmetry, a detonation in the center of the room, the blast pattern is enormously complex. Simulations were made of tests conducted at the BOP Test Site in which an instrumented cylinder was used to collect blast loading distribution on a man-like thorax. The simulation was able to quantitatively reproduce the highly irregular load distribution seen. (Chan and Klein, 1994)

Another common way in which complex waves arise is from externally generated blast waves entering an enclosure through an opening. The example studied was the overpressure in the cab of the M108/109 caused by the firing of its 155 mm howitzer. Calculations were made with EITACC-BL by both JAYCOR and WRAIR to determine ways in which the pressures seen in field tests could be simulated in nonweapon tests at the BOP Test Site. (Kan, 1994a).

Another common military geometry arises from weapons fired from enclosures. The source of the blast is the exhaust of the weapon, which can be difficult to characterize. To

provide generic guidance, MRMC conducted a series of tests in which the blast from an external detonation was directed into a tube that extended to the center of a closed room. EITACC simulations of the geometry, including the detailed blast capturing apparatus, produced excellent agreement with the multiple pressure gauges within the room and showed that local blast concentration points exist, including one near where the operator of the weapon would be.

To demonstrate the power of simulation, the characterization of the RAAWS weapon developed from free-field data was used in a calculation that placed the weapon in a firing position out of a cylindrical enclosure. See Figure 3. Although there is no corresponding physical experiment to confirm the results, the behavior is similar to that seen in the idealized tests and demonstrates how the hazard assessment can be extended to new situations without expensive field tests. (Chan and Dudkin, 1995).

Finally, blast overpressure can occur in vehicles that have been “defeated” by anti-vehicle weapons. Because of internal protection devices, injury is often limited to those individuals in the direct line-of-flight of the projectile, so that blast becomes a significant and meaningful injury concern. With the assistance of the Swedish Defense Establishment, a simulation of the blast inside a “defeated” cylinder was made that agreed well with test data. (Kan, 1995b).

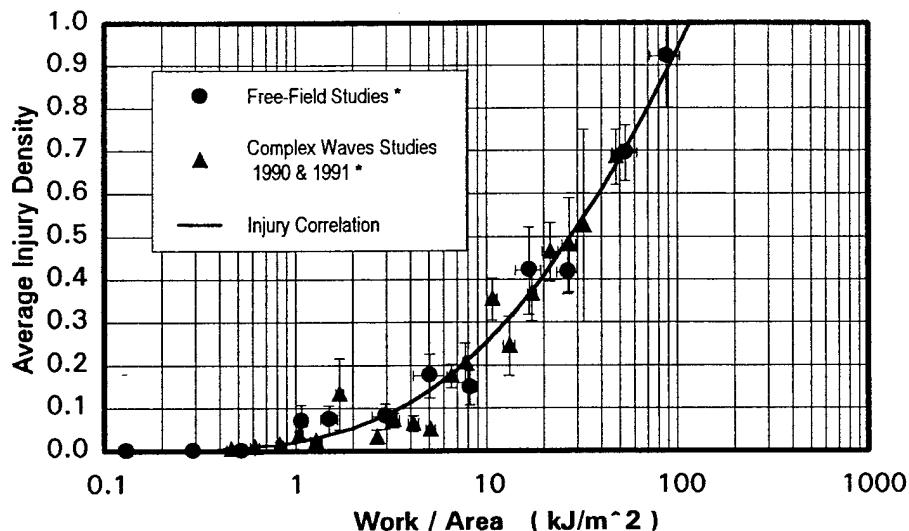


Figure 3. EITACC simulation of blast from a RAAWS weapon fired from an enclosure.

## Injury Modeling

*Generalized Fatigue Model.* In the original formulation of a generic blast overpressure response model (Stuhmiller, 1986), the concept of biomechanical fatigue was introduced to explain the increased injury that accompanies repeated exposure. Working with an analogy to nonbiological materials, the critical stress causing failure was assumed to decrease exponentially with the number of exposures until an "ultimate strength" was reached. This concept has been advanced by adopting the Paris equation of fatigue (Paris et al., 1961) and calibrating the coefficients against actual animal test results for the URT. (Ho, 1995).

*Surrogate Model Tests.* Under blast loading, the rapid motion of the chest wall compresses the parenchyma in the vicinity of the pleural surface and raises the local pressure. This pressure is a significant force in slowing down the chest wall as well as being the source of the internal compression wave that does lung damage. The pressure must be accurately represented in the modeling to obtain the correct chest wall dynamics. Previously, a model using surrogate materials (piston driven foam-filled tube) was found to reproduce the chest wall dynamics, but the pressure and acceleration measurements were difficult and confirmation of the complete dynamics was incomplete (Yu et al., 1990).

By using an instrumented falling weight to deliver the impact loading and measuring the motion of both the weight and the piston it is possible to measure all quantities in the energy equation. (Yu, 1993). Over 60 tests were conducted that confirmed the linear relation between lung pressure and chest wall velocity. Additional tests using Kevlar material showed that 13% more work was done on the foam. These values are statistically significant ( $p < 0.01$ ) and similar to increased injury levels seen in field tests (Young et al., 1985).

*Lung Injury Model.* The earliest investigations of lung injury showed the role played by the parenchymal pressure wave and the surrogate model tests provided the mechanistic link of this wave to the chest wall motion. A single degree of freedom model of the chest wall motion allows calculation of the amount of irreversible work generated by the external blast loading. Normalizing the work by the animal's body mass, proved to correlate lethality results for all species. The resulting, dimensionless relations were compared with all injury and lethality data available. Incidence of gross lung injury for the exposed population for all levels of severity as well as for areal extent of injury, (Figure 4) could be correlated with normalized work. (Stuhmiller et al., 1996)

*Finite Element Modeling from Medical Imaging.* In a collaborative effort between MRMC and the National Highway Traffic Safety Administration (NHTSA), mathematical techniques were developed to generate anatomically exact models of the skull from CT images.(Vander Vorst, 1994). These techniques are part of a concerted effort on the part of NHTSA to evaluate and improve head injury criteria and to implement these findings in future crashworthiness tests (Bandak et al., 1995)

The image-based finite element modeling techniques are being adapted to other organs, the first being the construction of a multidimensional thorax model. (Masiello et al., 1995). Using the collection of images known as the "Visible Man" (National Library of Medicine), a mathematical mapping of model to image coordinates was developed. The resulting three-dimensional model of the thorax was subjected to external blast loading and the resulting dynamics showed the complex internal pressure waves within the lung and against the heart.

## **Health Hazards Assessment**

*Statistical Basis for HHA.* The goal of the HHA methodology is to define the level of risk associated with a particular blast overpressure exposure. One part of the effort is to understand the relation of the external forces to a specific organ injury. The other part is to translate those results into an estimate of risk to a population from all injury paths.

Historically, nonauditory HHAs were based on an estimate of the "threshold" injury to a single organ system (usually the lung). The threshold level was not established by statistical analysis, but by an estimate intended to be "just below" (in peak pressure-duration coordinates) of any injury previously seen. The fraction of the population that will be injured below this level will depend on the number of animals used in the tests.

A completely general, statistically-based HHA methodology has been formulated. The HHA is stated in the form "a given blast overpressure environment will produce, with Y% confidence, X% incidence in a population of any one of a number of unacceptable consequences." The mathematical formulation takes into account the standard errors in the correlation of injury with the predicted biomechanical factor and the standard error in the



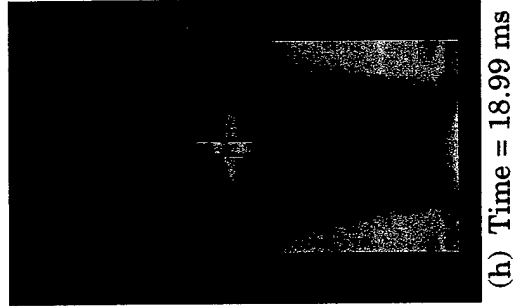
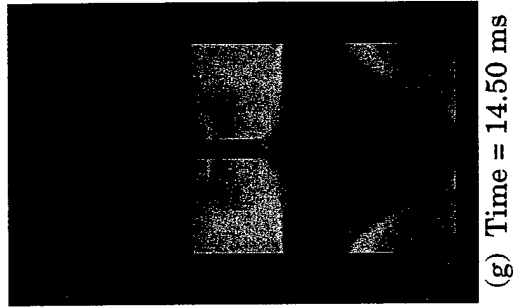
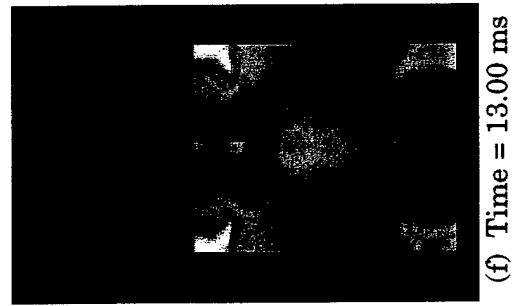
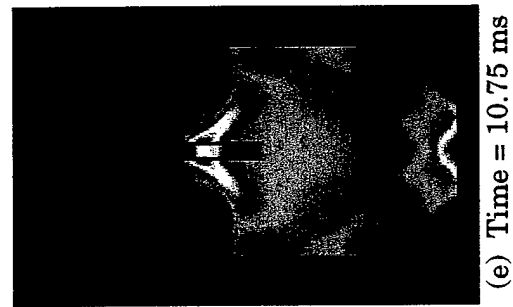
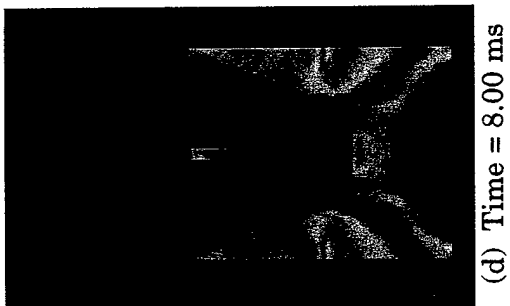
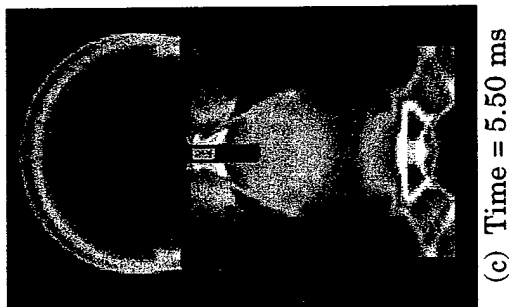
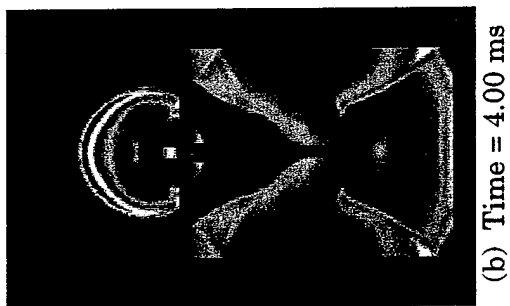
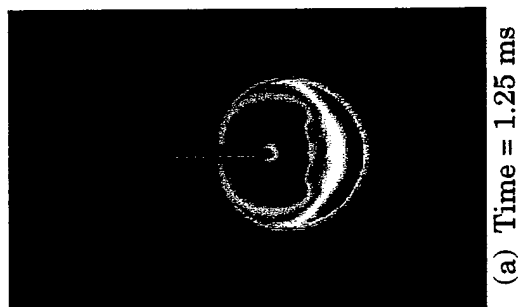
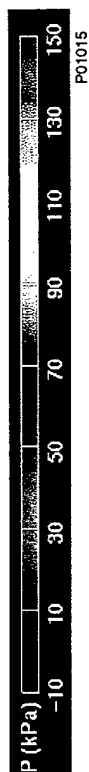


Figure 4. Correlation of observed animal injury to the lung with the total work done on the lung as computed by the pleural surface biomechanical model.

measurement of the blast environment. (Kan, 1994b). The heart of the mathematics is the convolution of each statistical distribution, which must be integrated numerically.

*INJURY Software.* To assist the process of making a health hazards assessment, the INJURY software was developed. Up to four pressure time histories, representing the loading around the body, can be selected in digital form. The software will compute the normalized work from each loading and the total lung injury predicted. If multiple sets of data are available, the program will compute the normalized work for each set and the statistics of the injury. The output gives the predicted range of incidence of lung injury in the population for any confidence level. (Ho, 1995)

*Nonlethal Weapons.* Recently, there has been a need to evaluate injury from nonpenetrating impacts delivered by "nonlethal" weapons. It is likely that, in addition to fracture, these impacts will produce soft tissue injury to the lungs and internal organs by the same mechanisms responsible for blast overpressure injury. The difference is that the loading is localized to the point of impact, rather than being distributed around the body. Although more research into the thorax dynamics is required to provide a satisfactory understanding and prediction of risk, a preliminary link between blunt impact and normalized work has been developed. (Kan, 1995c)

# Discussion

## Summary of Accomplishments

The main objectives of the research effort have been met. A statistically valid assessment of organ damage has shown that all of the major air containing organs (URT, lung, and GI tract) have similar injury thresholds. Under multiple exposures, the GI tract may be the most susceptible organ system. Injuries are primarily seen on the blast side in free-field cases, but occur on both sides in enclosures. There is a pattern of injury to organs near the diaphragm, suggesting a possible dynamic role.

Computational fluid dynamics (CFD), in particular the EITACC software, has been successful in simulating a wide variety of blast environments, both in the free-field and in enclosures. The various exposure conditions can be divided into a hierarchy of geometries which allows a unifying perspective.

Normalized, irreversible work done on the lung by the motion of the chest wall has proven to be an excellent correlate of pathology and lethality seen in animal tests. Computed from dynamic equations that can be used in all blast environments and for all large animal species, a truly general injury prediction has emerged.

Finally, a statistically-based methodology for determining population risk and corresponding level of confidence has been produced. The INJURY program helps automate the injury calculations and hazard assessment and when it is released to the research community, will assure a uniformity in risk assessment.

## Open Issues

*GI Tract Injury.* The prevalence of GI tract injury is somewhat unexpected and raises the possibility that this organ system may be the controlling factor in making hazard assessments. Even if it is not the dominant factor, the potential for combined respiratory and GI injury complicates the medical treatment options. Since the animal model used in all of the BOP Test Site experiments was a ruminant, the sheep, a question is raised as to whether the animal's large, gas-filled stomachs influenced this trend, making GI injury more or less predominant than it would be in man. Resolution of the thoracic-abdominal dynamics between species is required.

*Performance.* The damage done by blast overpressure can be extensive, but has primarily been described by its pathology. Measurements have shown that there are striking physiological changes, which can be aggravated by exercise. Since military exposure to blast, either in training or combat, undoubtedly is accompanied by exertion, consequences to performance may be significant. A quantitative link between blast environment and physiological effects is required.

*Blunt Trauma.* The soldier faces hazards from blunt trauma, including nonlethal weapons, nonpenetrating ballistic impact, and vehicular impacts, that undoubtedly produce soft tissue injuries similar to that of blast overpressure. Since the mechanistic coupling of the internal pressure wave is understood, there is an opportunity to expand the predictive ability of the models and generalize the health hazards assessments.

*Combined Injury.* Just as exertion will accompany most blast overpressure exposures, it is likely that the soldier will be exposed to toxic gasses in any enclosed situation. Since both overpressure and toxic gas attack the respiratory system, it is likely that there will be a synergistic, deleterious effect of the combination. Investigation of these effects is required.

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